

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE PATENT

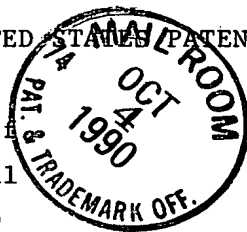
In re the application of

William R. PILGRIM et al

Serial No. : 07/403,280

Filed : June 9, 1989

For : PROCESS FOR THE PREPARATION OF 1-ADAMANTANE DERIVATIVES



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Group Art Unit : 126  
Examiner : Paul J. KILLOS

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DECLARATION

I Joël LAGIERE, declare :

1. THAT I am a French citizen residing at 1 Porte de l'Adous, Sophia Antipolis, 06560 VALBONNE, FRANCE ;

2. THAT I have a Doctorate degree in Organic Chemistry from University of BORDEAUX ;

3. THAT I have been employed by Centre International de Recherches Dermatologiques (CIRD), the assignee of the present application, since April 21, 1986 and that I am currently a Team Leader in the Synthetic Chemistry Laboratory ;

4. THAT I am well acquainted, as co-inventor, with the invention disclosed in U.S. Patent Application Serial No. 07/403,280 filed June 9, 1989 in the name of PILGRIM et al and entitled : PROCESS FOR THE PREPARATION OF 1-ADAMANTANE DERIVATIVES ;

5. THAT I am also well acquainted with the prior art cited in the Office Action mailed March 28, 1990, ie U.S. Patent No. 4,087,410 (DOMINIANNI et al) ;

6. THAT under my direction, experiments were carried out to compare the preparation of 1-hydroxy-2,6-dimethoxy-4-adamantyl benzene (column 6, line 23 of DOMINIANNI et al) starting from 2,6-dimethoxyphenol

(a) following the first step of the method of DOMINIANNI et al using 1-adamantanol and

(b) following the method of the present application Serial No. 07/403,280 using acetoxy-1-adamantane ;

7. THAT the DOMINIANNI et al procedure was carried out three times (each time using a chosen temperature and reaction time) as follows :

(i) 1.52 g of 1-adamantanol, 20 ml of tetrahydrofuran, 1.54 g of 2,6-dimethoxyphenol and 2 ml of methanesulphonic acid were placed in a three-necked flask under an atmosphere of nitrogen ;

(ii) the flask was heated and stirred at fixed temperature and for a fixed duration (see table below) ;

(iii) thereafter, the reaction mixture was extracted using ethyl acetate followed by washing the organic phase in water saturated with sodium bicarbonate and then drying over magnesium sulphate ;

(iv) after filtration, the solvents were evaporated under reduced pressure and any product formed was obtained as a chestnut brown deposit ;

(v) the chestnut brown product was chromatographically purified on a silica column using 40/60 dichloromethane/hexane as eluant followed by double recrystallisation in hexane ;

(vi) following filtration on sintered glass the beige crystals obtained were dried overnight at 30°C in a ventilated oven and the yield noted (see table below) ;

8. THAT the procedure according to the present invention was as follows :

(i) 1.94 g of acetoxy-1-adamantane was dissolved completely in 10 ml of n-heptane and 50 ml of cyclohexane in 250 ml three-necked flask under an atmosphere of nitrogen ;

(ii) 0.3 ml of concentrated sulphuric acid was added dropwise ; at 20°C, 1.54 g of 2,6-dimethoxy phenol was added while stirring for 8 hours ;

(iii) thereafter the reaction mixture was extracted using ethyl acetate followed by washing the organic phase in water saturated with sodium bicarbonate and then drying over magnesium sulphate ;

(iv) after filtration the solvents were evaporated under reduced pressure to obtain the crude product ;

(v) the crude product was chromatographically purified over a silica column using a 40/60 dichloromethane/hexane eluant followed by recrystallisation in hexane ;

(vi) following filtration on sintered glass, the white crystals obtained were dried overnight at 30°C in a ventilated oven and the yield noted (see table below) ;

9. THAT where product was obtained, its melting point was measured to confirm identity (see table below) ;

10. THAT the results of the experiments are given in the following table :

	reaction temp/°C	reaction duration/hrs	yield /%	melting point/°C
DOMINIANNI et al	50 -> 65*	48	37.8 (1.09g)	115-117
ditto	65	8	< 5% **	
ditto	50	8	0	n/a
Present Invention	20	8	38.2 (1.1g)	116-117

TABLE

\* 50°C for 24 hrs followed by 65°C for 24 hrs

\*\* estimated by thin layer chromatography

11. THAT in order to purify the product in the first DOMINIANNI et al experiment it was necessary to effect two recrystallisations from hexane leading even then to a discoloured (beige/pink) product ;

12. THAT this difficulty in purification was because not all the starting products (1-adamantanol and 2,6-dimethoxyphenol) had reacted and at least 35 % w/w of 2,6-dimethoxyphenol remained bound up in the final product ;

13. THAT, on the other hand, for an equivalent yield (about 38 %) of final product obtained using the method according to the present invention, a white (purer) substance not polluted with starting material was obtained ;

14. THAT the results show that using the process according to the present invention, it is possible to produce a yield equivalent to the DOMINIANNI et al process but at much lower temperature (ambient) and in much less time ;

15. THAT the DOMINIANNI et al process carried out in the mild conditions of the present invention yields little or no product ;

16. THAT I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine of imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date : 24 septembre 1990

Signature : Joël Laggière  
Joël LAGIERE